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Efficacy and Safety of NOACs Compared With VKAs for Patients With Atrial Fibrillation After Transcatheter Aortic Valve Implantation: A System Review and Meta-Analysis

Junye Ge, MD[1], Wenqiang Han, MD, PhD[1], Chuanzhen Ma, MD[1], Kellina Maduray, MD[1], Tongshuai Chen, MD, PhD[1], and Jingquan Zhong, MD, PhD, FACC[1,2]

Abstract

Novel oral anticoagulants (NOACs) are preferentially recommended in patients with nonvalvular atrial fibrillation (AF) for stroke prevention over vitamin K antagonists (VKAs). However, the evidence regarding the efficacy and safety of NOACs versus VKAs after transcatheter aortic valve implantation (TAVI) in patients with AF is very rare. Pubmed, Embase, Web of science, and Cochrane Databases were searched for eligible studies published before May 19, 2022. A total of 11 studies were included in this meta-analysis involving 27 107 patients. Regarding primary outcomes, there were no differences between NOACs and VKAs in all-cause mortality (*RR*: 0.84, 95% *CI*: (0.69, 1.02)) and stroke (*RR*: 1.00, 95% *CI*: (0.85, 1.19)). With respect to secondary outcomes, NOACs were associated with reduced incidence of bleeding (*RR*: 0.77, 95% *CI*: (0.71, 0.83)) and intracranial bleeding (*RR*: 0.57, 95% *CI*: (0.39, 0.83)), whereas no significant differences were found in major or life-threatening bleeding (*RR*: 0.98, 95% *CI*: (0.82, 1.17)) and myocardial infarction (*RR*: 1.37, 95% *CI*: (0.83, 2.26)). Our meta-analysis revealed the safety and efficacy of NOACs may be superior to VKAs in AF patients undergoing TAVI.

Keywords

transcatheter aortic valve implantation, atrial fibrillation, anticoagulant, novel oral anticoagulant, vitamin K antagonist

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Introduction

Transcatheter aortic valve implantation (TAVI) has become the preferred strategy for the treatment of symptomatic severe aortic stenosis in older adults, with indications broadened to include intermediate or low-risk patients.[1,2] Atrial fibrillation (AF) is one of the most common persistent arrhythmias, with an annually increasing incidence, which is known to be closely associated with aortic stenosis.[3-5] The prevalence of previous AF is as high as 51.1% among patients undergoing TAVI, whereas the new-onset AF rate ranges from 1% to 32%, increasing the risk of thromboembolic and bleeding events.[5,6] The

[1] The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Department of Cardiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China
[2] Department of Cardiology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China

Corresponding Authors:
Jingquan Zhong, Department of Cardiology, Qilu Hospital Affiliated to Shandong University, 107 Wen Hua Xi Road, Jinan 250012, China.
Email: 198762000778@email.sdu.edu.cn

Tongshuai Chen, Department of Cardiology, Qilu Hospital Affiliated to Shandong University, 107 Wen Hua Xi Road, Jinan 250012, China.
Email: chentongshuai@163.com.

majority of AF patients require oral anticoagulants (OACs), such as vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs), on a long-term basis to reduce thromboembolic events. Due to their superior efficacy and safety, NOACs has been widely used in clinical practice, which has become the preferred choice for stroke prevention in patients with nonvalvular AF.[7,8]

Currently, evidence regarding the efficacy and safety of NOACs versus VKAs after TAVI in patients with AF is very rare, thereby under debate. Throughout the available clinical evidence, the results were also controversial. A multicenter European study enrolled 962 patients undergoing TAVI, more than 99% of whom suffered from AF.[9] The findings revealed that the composite outcomes, including any cerebrovascular event, all-cause mortality, and myocardial infarction, were significantly higher in NOACs than in VKAs during 1-year follow-up. In contrast, the largest observational study, including 21 131 AF patients from America, compared the clinical outcomes of NOACs versus VKAs after TAVI.[10] The results demonstrated that the AF patients prescribed NOACs experienced lesser bleeding, intracranial hemorrhage or death events with comparable stroke events after TAVI during 1-year follow-up. On the one hand, some studies proved that NOACs were inferior to VKAs with increased composite outcomes or major bleeding events[9,11]; on the other hand, others supported that NOACs were equivalent or superior to VKAs in all-cause mortality, stroke, bleeding, and so on for patients with AF after TAVI.[10,12,13] Due to the large difference in results, we analyzed the available clinical studies[9-19] data to systematically evaluate the efficacy and safety of NOACs versus VKAs after TAVI in patients with AF to provide a reference for clinical treatment.

Methods

This meta-analysis was performed on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] A review protocol was not registered for this meta-analysis.

Search Strategy

Pubmed, Embase, Web of science, and Cochrane Databases were fully searched for eligible studies published before May 19, 2022. The detailed search strategy is summarized in Table 1 in the online supplementary materials.

Study Selection and Quality Assessment

The inclusion criteria: (1) The subjects were TAVI recipients with AF (AF patients >90% of the total subjects). (2) The study included comparisons between NOACs and VKAs groups. The exclusion criteria: (1) No-AF patients or AF patients <90% of the total subjects. (2) Studies that failed to report relevant data regarding NOACs and VKAs groups. The study quality was independently assessed by two authors based on the Newcastle-Ottawa Scale[21] (observational study) or Cochrane Collaboration Risk of Bias Tool[22] (randomized controlled trial). Any inconsistencies were determined after discussion by two authors.

Data Extraction and Summary Outcomes

The required data were independently extracted by the two authors, including first author's name, year, country, male proportion, number of patients, CHA2DS2-VASc score, HAS-BLED score, duration of follow-up, specific outcome values and so on. All-cause mortality and stroke (new-onset stroke) were evaluated as primary outcomes. Secondary outcomes included bleeding, major or life-threatening bleeding, intracranial bleeding and myocardial infarction. The events and total counts between the NOACs and VKAs group as well as the relative risks (*RRs*) with 95% confidence intervals (*CIs*) were extracted or computed.

Statistical Analysis

The effect size was expressed as *RRs* with 95% *CIs*. The heterogeneity among studies was assessed by the Q test. $I2 \geq 50\%$ was regarded as high heterogeneity, while $I^2 < 50\%$ indicated low heterogeneity. If $I^2 \geq 50\%$, the random effect model was used. Otherwise, the fixed effect model was applied for meta-analysis. The high heterogeneity among the studies was further analyzed by the Galbraith star chart. Univariate meta-regression was performed to explore the influencing factors of heterogeneity. Sensitivity analysis was performed to assess the stability of the findings. Publication bias was evaluated by Egger's test. A $P < .05$ was considered statistically significant in all analyses. The software Stata version 15.1 was used in this meta-analysis.

Results

Study Selection and Quality Assessment

The detailed literature search is shown in Figure 1. A total of 2070 pieces of literature were initially retrieved. One randomized controlled trial and 10 observational studies were finally included in this meta-analysis after multiple screenings. A high quality was achieved for the randomized controlled trial by Cochrane Collaboration Risk of Bias Tool (Figure 1 in the online supplementary materials). Based on the Newcastle-Ottawa scale, the scores of the included observational studies ranged from 5 to 9, indicating that the studies achieved moderate to high quality (Table 2 in the online supplementary materials).

Study Characteristics

The baseline characteristics of the included studies are listed in Table 1. Most of the studies have been published in the last five years from multiple countries. This meta-analysis included 27 107 patients. Only one study included more than 10 000 patients, while the other studies had less than 2000 patients.

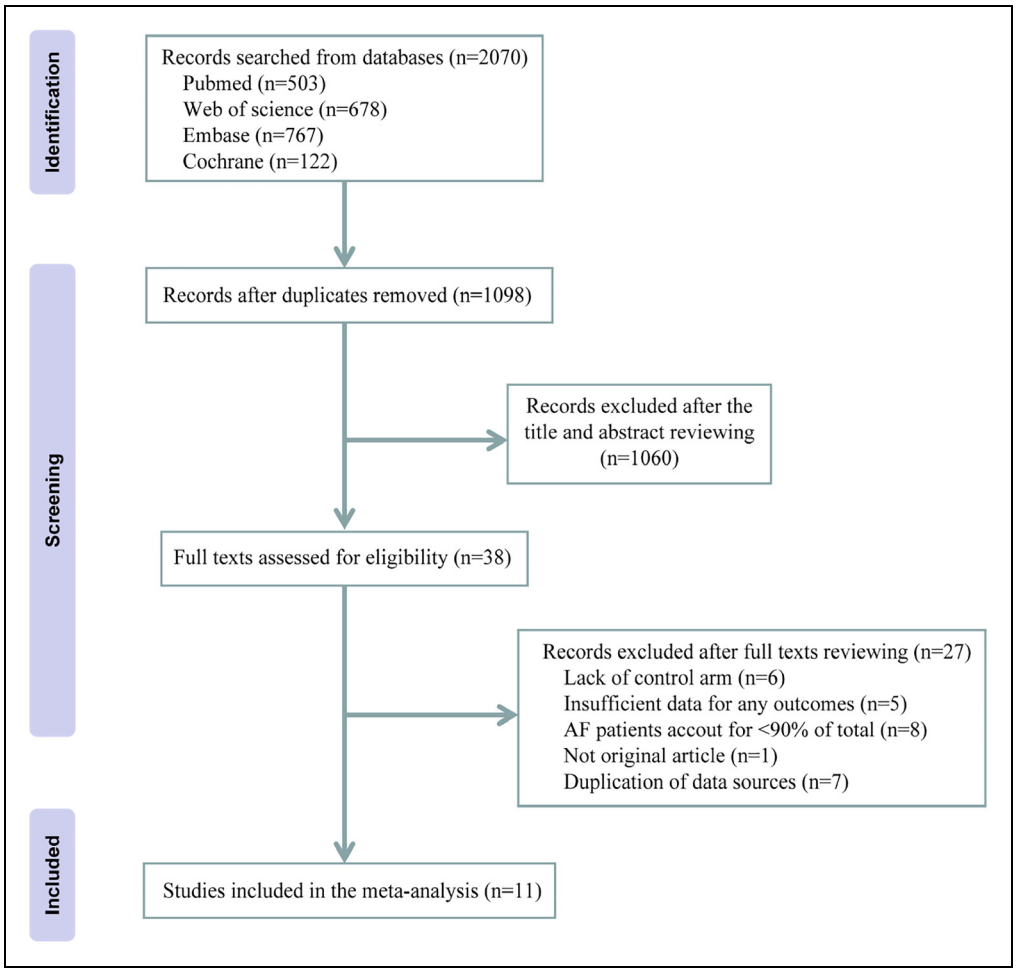

Figure 1. Flow chart of literature search.

The studies also differed greatly in the percentage of male participants and the number of patients enrolled. The majority of patients receiving TAVI were over 80 years old, among whom hypertension was prevalent. In terms of the overall patients, a higher CHA2DS2-VASc score was observed, indicating a higher risk of thromboembolic events.

Summary Outcomes

Primary outcomes. All-cause mortality data were available from 10 studies (Figure 2A). The results showed that the all-cause mortality in the NOACs group was lower than that in the VKAs group, but there was no significant difference (*RR*: 0.84, 95% *CI*: (0.69, 1.02)). High heterogeneity was observed ($I^2 = 61.6\%$, $P = .005$).

Stroke data from nine studies were analyzed (Figure 2B). Meta-analysis showed comparable stroke rates between the NOACs and VKAs group with no significant difference (*RR*: 1.00, 95% *CI*: (0.85, 1.19)). There was no heterogeneity across studies ($I^2 = 0.0\%$, $P = .607$).

Secondary outcomes. Bleeding data were reported in eight studies (Figure 3A). It was found that bleeding events were less frequent in the NOACs group than in the VKAs group (*RR*: 0.77, 95% *CI*: (0.71, 0.83)). Low heterogeneity was observed ($I^2 = 44.8\%$, $P = .080$).

Seven studies provided data on major or life-threatening bleeding (Figure 3B). There were similar event rates in the NOACs group compared to VKAs group (*RR*: 0.98, 95% *CI*: (0.82, 1.17)). There was low heterogeneity across studies ($I^2 = 30.6\%$, $P = .194$).

Data from five studies were evaluated regarding intracranial bleeding (Figure 3C). The NOACs group had a significantly lower rate of intracranial bleeding compared with the VKAs group (*RR*: 0.57, 95% *CI*: (0.39, 0.83)). Low heterogeneity was observed ($I^2 = 3.6\%$, $P = .386$).

Four studies published data on myocardial infarction (Figure 3D). The meta-analysis showed no significant difference in myocardial infarction between the NOACs and VKAs groups with a trend toward increased events in the NOACs group (*RR*: 1.37, 95% *CI*: (0.83, 2.26)). There was no heterogeneity across studies ($I^2 = 0.0\%$, $P = .781$).

Heterogeneity Analysis

Given the high heterogeneity observed with all-cause mortality, we explored the sources of heterogeneity qualitatively and

Table 1. the Baseline Characteristics of the Included Studies.

Author	Year	Country	Total Population	Number (NOAC)	Number (VKA)	NOAC Species	Age (mean)	Male (%)	CHA2DS2-VASc (mean)	HAS-BLED	Follow-up	Hypertension (%)	Diabetes (%)	Antiplatelet Theraphy
Seeger	2017	Germany	272	141	131	Apixaban	81.3	50.7	4.9	3.1	12 months	-	32.4	-
Alraies	2017	American	170	58	112	-	-	-	-	-	1 year	-	-	-
Geis	2018	Germany	326	154	172	Multiple	83.1	47.2	4.7	2.8	6 months	93.6	31.9	None
Mangner	2018	Germany	598	182	416	Multiple	80 (median)	43.8	5.5	3	12 months	97	48.2	-
Jochheim	2019	Multinational	962	326	636	Multiple	81.3	47.5	≥2	-	1 year	89.6	32.3	None, single or dual
Butt	2019	Denmark	735	219	516	Multiple	82 (median)	53.7	4.9	3.3	369 days	88.2	22.3	None, single or dual
Kosmidou	2019	Multinational	933	155	778	-	82.8	65.6	5.6	-	2.8 years	91.7	35.3	-
Okoh	2019	American	151	31	121	Rivaroxaban	-	-	-	-	36 months	-	-	-
Kawashima	2020	Japan	403	227	176	Multiple	84.4	33.3	5.1	2.7	568 days	76.2	24.3	None, single or dual
Tanawuttiwat	2022	American	21 131	8127	13 004	Multiple	83 (median)	56.7	3	-	1 year	91.7	36.9	-
Van Mieghem (ENVISAGE-TAVI AF)	2021	Multinational	1426	713	713	Edoxaban	82.1	52.5	4.5	-	530 days	91.4	37.0	None, single or dual

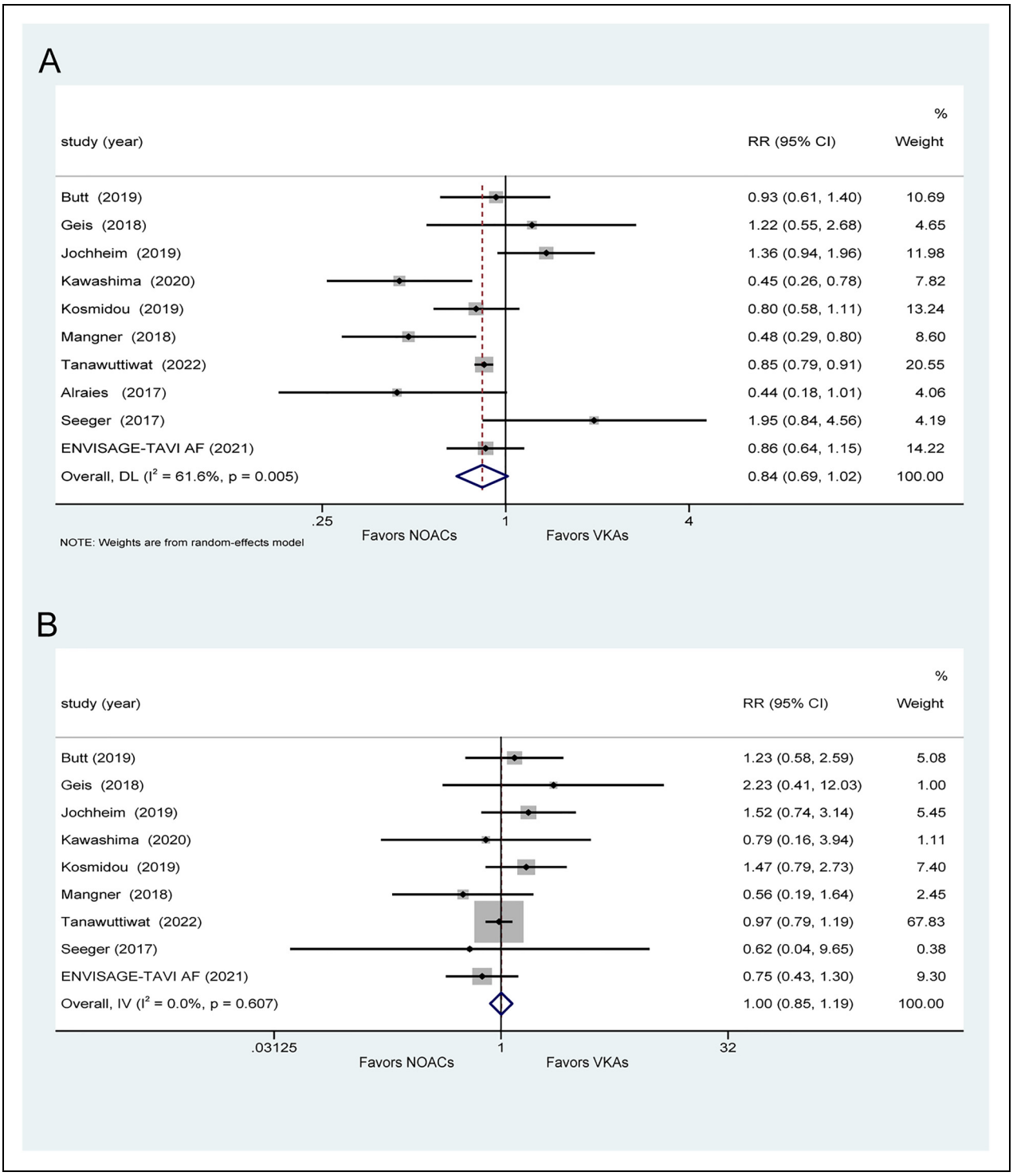

Figure 2. Forest plot to compare NOACs with VKAs in primary outcomes including all-cause mortality (A) and stroke (B).

quantitatively by using the Galbraith star chart and meta-regression. As seen in the Galbraith star chart (Figure 2 in the online supplementary materials), the high heterogeneity may be related to the studies including Jochheim et al, Mangner et al, and Kawashima et al studies. After excluding these studies, meta-analysis (Figure 3 in the online supplementary materials) showed a significant reduction in heterogeneity ($I^2 = 14.9\%$, $P = .316$) and change in result (*RR*: 0.85, 95% *CI*: (0.80, 0.91)). The univariate meta-regression analysis did not find the possible source of heterogeneity, for instance total population, age, male, hypertension, diabetes, follow-up, and CHA2DS2-VASc (Table 3 in the online supplementary materials).

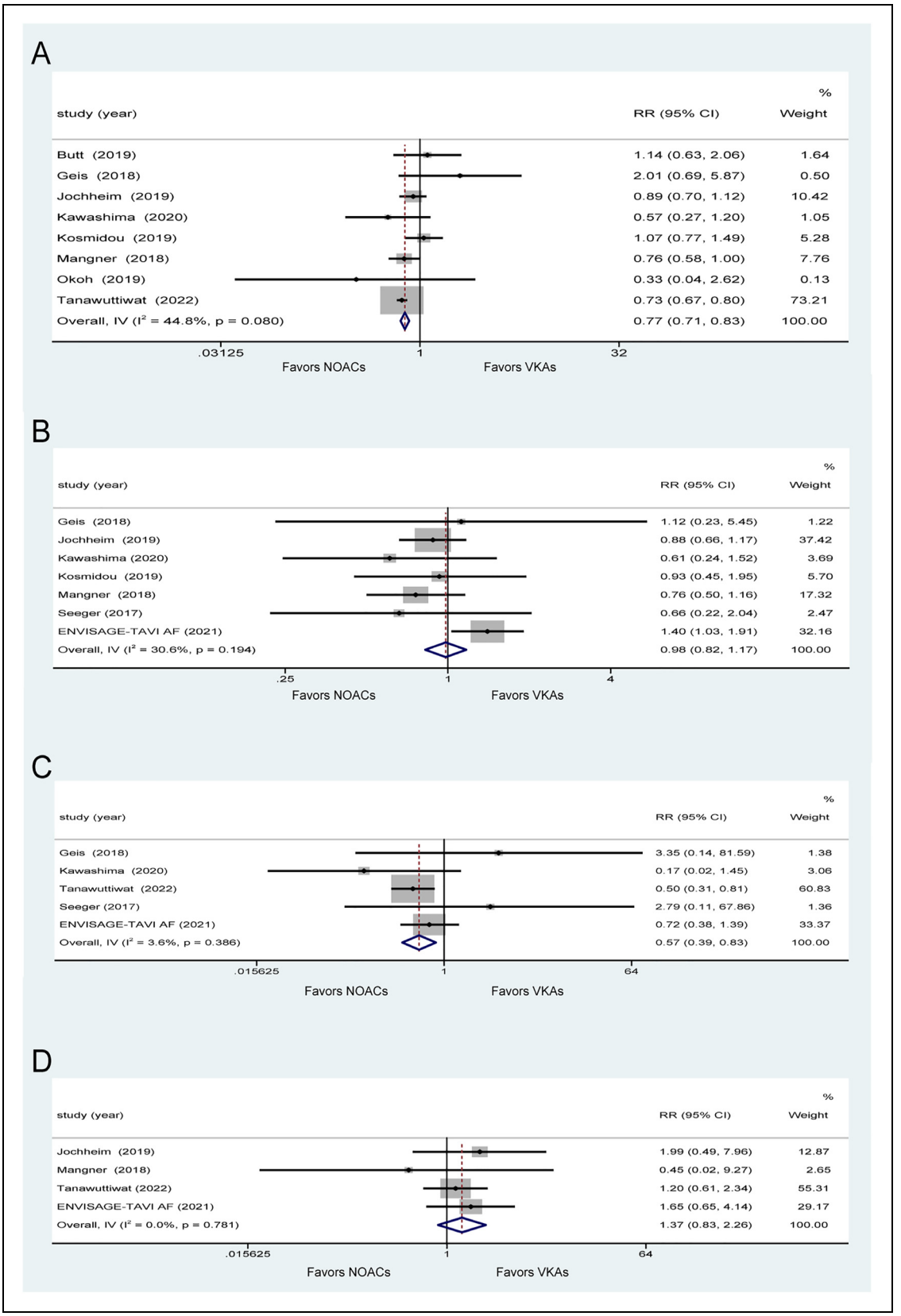

Figure 3. Forest plot to compare NOACs with VKAs in secondary outcomes including bleeding (A), major or life-threatening bleeding (B), intracranial bleeding (C) and myocardial infarction (D).

Sensitivity Analysis

Sensitivity analysis performed on all-cause mortality, bleeding and intracranial bleeding revealed a significant change in observed results (Figure 4A-C in the online supplementary materials). For all-cause mortality, the result was statistically significant after excluding Jochheim et al study (*RR*: 0.79, 95% *CI*: (0.65, 0.95)) or Seeger et al study (*RR*: 0.81, 95% *CI*: (0.67, 0.98)). Based on the exclusion of Tanawuttiwat et al study, no significant differences were found between NOACs and VKAs in bleeding (*RR*: 0.89, 95% *CI*: (0.77, 1.03)) and intracranial bleeding (*RR*: 0.71, 95% *CI*: (0.39, 1.29)). In the remaining outcomes, the results did not change significantly following the sensitivity analysis (Figure 4D-F in the online supplementary materials).

Bias Assessment

No publication bias was observed by Egger's test in all-cause mortality ($P = .895$), stroke ($P = .701$), bleeding ($P = .226$), and major or life-threatening bleeding ($P = .428$). Due to the small number of included studies, publication bias was not evaluated in other outcomes.

Discussion

This meta-analysis comprised all studies reporting AF patients undergoing TAVI and studies with AF patients accounting for more than 90% of all TAVI patients, so as to minimize the impact of other disorders with anticoagulation-related indications while ensuring sufficient number of studies. Regarding the primary outcomes, NOACs had no significant difference from VKAs in terms of all-cause mortality and stroke. With respect to secondary outcomes, NOACs were associated with a reduced incidence of events in bleeding and intracranial bleeding, whereas no significant differences were found between NOACs and VKAs for major or life-threatening bleeding and myocardial infarction.

The anticoagulant regimen after TAVI is complex. Low-dose aspirin is usually used to prevent valve thrombosis in TAVI patients without anticoagulant indications.[1,2] The administration of antithrombotic regimens in TAVI patients with anticoagulant indications remains complex and controversial. The reason for added antiplatelet therapy in addition to anticoagulation may be to reduce periprocedural thromboembolic events during valve endothelialization in AF patients after TAVI.[23] In the Popular-TAVI trial, Cohort B confirmed that anticoagulants alone were associated with fewer major bleeding events compared with anticoagulants plus clopidogrel after TAVI in patients with anticoagulant indications, with comparable incidence of stroke, myocardial infarction, or all-cause death events.[24] A multicenter observational study has come to a similar conclusion that warfarin plus antiplatelet agents increased the risk of major bleeding after TAVI in AF patients, and failed to reduce stroke or adverse cardiovascular events occurrence, compared with warfarin alone.[25] Based on this, guidelines and expert consensus recommend long-term anticoagulation in patients with anticoagulant indications after TAVI, and OACs alone is preferred.[1,2,26]

Multiple randomized controlled trials indicated that NOACs reduced the incidence of stroke/transient ischemic attack and the risk of major bleeding compared to VKAs in patients with nonvalvular AF,[27-30] which has been recommended by guidelines for the management of AF.[8] However, whether VKAs or NOACs are the preferred anticoagulant therapy for patients with AF undergoing TAVI is still unknown. The 2020 ACC/AHA Guideline indicated that NOACs can be used as an alternative to VKAs after 3 months of biologic valve replacement in patients with AF.[2] The ENVISAGE-TAVI AF trial included 1426 AF patients undergoing TAVI to compare the efficacy and safety of edoxaban versus VKAs.[11] The results confirmed that edoxaban was noninferior to VKAs in terms of composite adverse clinical events; however, the patients treated with edoxaban had a higher incidence of major bleeding, mainly major gastrointestinal bleeding.[11] The ATLANTIS trial demonstrated the use of apixaban after TAVI was not superior to the standard antithrombotic therapy in patients with or without anticoagulation indication, based on the net clinical benefit.[31] In the subgroup analysis of apixaban versus VKAs, AF patients accounted for less than 90% of TAVI patients,[31] so the trial was not included in our meta-analysis. To date, the latest guidelines do not specify the preference of NOACs or VKAs for anticoagulant therapy in AF patients after TAVI.[1]

Although the meta-analyses on the clinical outcomes of NOACs versus VKAs after TAVI in patients with AF have been published,[32,33] the search was more comprehensive with an increase in the number of patients enrolled and only studies with AF patients accounting for more than 90% of all TAVI patients were included in our meta-analysis. Most importantly, the results of our meta-analysis differed from those meta-analyses. A meta-analysis found that NOACs had lower risks of all-cause mortality and bleeding than VKAs at 1 year after TAVI in AF patients.[33] Another meta-analysis conducted by Memon et al showed no significant difference in stroke or systemic embolism, all-cause mortality, major bleeding, intracranial hemorrhage, and myocardial infarction between NOACs versus VKAs for AF patients undergoing TAVI.[32] Our meta-analysis revealed that the patients prescribed NOACs had a lower incidence of bleeding and intracranial bleeding. However, sensitivity analyses found that the effects of NOACs and VKAs were equivalent in bleeding and intracranial bleeding after the exclusion of Tanawuttiwat et al study. The largest observational study by Tanawuttiwat et al was not included in prior meta-analysis.[32] Interestingly, the patients prescribed NOACs tended to have a lower incidence of all-cause mortality with the *RRs* less than 1 despite no statistical difference. Qualitative analysis showed that the three studies might be the source of the large heterogeneity of all-cause mortality, yet meta-regression did not find the specific factors leading to heterogeneity. Considering the existing clinical studies and meta-analyses, the safety and efficacy of NOACs were not inferior to VKAs in AF patients undergoing TAVI. Moreover, due

to the inherent disadvantages of VKAs, such as the narrow therapeutic window, high compliance and food interactions,[34] NOACs are more popular among clinicians. Our meta-analysis demonstrated that NOACs were a feasible alternative for VKAs in AF patients after TAVI, which may benefit clinical decision-making.

Limitations

Our meta-analysis is subject to several limitations. The type of NOACs differed among the included studies. NOACs were not subdivided explicitly according to the type. The combined antiplatelet regimens varied greatly among different studies. The aforementioned factors may be a potential source of heterogeneity. All-cause mortality analysis revealed significant heterogeneity, and the results for bleeding and intracranial bleeding were less stable. As a result, caution must be exercised when interpreting these findings.

Conclusions

Our meta-analysis revealed the safety and efficacy of NOACs may be superior to VKAs in AF patients undergoing TAVI. Therefore, NOACs may be a viable alternative for VKAs after TAVI in AF patients, which may aid clinical decision-making.

Author Contributions

JG designed the study, selected literature, collected and analyzed data, and drafted the manuscript. WH, CM, and KM selected literature and collected and analyzed data. TC and JZ analyzed data and reviewed the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

Data Availability

All relevant data are presented in the review and supplemental material.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

Our institution did not require informed consent or ethical approval from the patients for reporting a systematic review and meta-analysis.

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ORCID iDs

Kellina Maduray https://orcid.org/0000-0001-9038-5212
Jingquan Zhong https://orcid.org/0000-0001-9547-4070

Supplemental Material

Supplemental material for this article is available online.

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